

CASE REPORT

Dialysis-associated allergic reactions during continuous renal replacement therapy and hemodialysis: A case report

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Abstract

Dialyzer reactions are long-appreciated complications of dialysis. Despite advances in dialysis machines and membranes, these life-threatening reactions still occur. It is imperative to recognize potential dialyzer reactions when assessing adverse dialysis events as reexposure to dialytic treatments could be life threatening. We present the case of a 72-year old woman with dialysis-requiring anuric acute kidney injury who experienced acute hypotension and cardiopulmonary arrest during both continuous renal replacement therapy and a subsequent hemodialysis treatment. We concluded that she had an anaphylactic reaction to an unidentified component of the dialysis equipment. Identification, work up, treatment, and reporting of dialyzer reactions are discussed in the context of this case.

Keywords: hemodialysis, dialyzer reaction, hypotension, allergic reaction, safety issues

INTRODUCTION

Dialysis-associated hypersensitivity reactions, both anaphylactic and anaphylactoid, are long-recognized complications of dialysis. The majority of cases relate to ethylene oxide (EtO)-sterilized equipment, cellulose membranes and

medications. Reactions generally present as acute events with symptoms such as flushing, pruritus, angioedema, pain, and shortness of breath.¹ However, clinical presentations vary, and the offending allergen may be challenging to identify. Herein, we describe a case of presumed dialysis hypersensitivity reactions that initially presented during continuous renal replacement therapy (CRRT) and recurred with hemodialysis (HD).

CASE HISTORY

A 72-year-old woman with a history of kidney transplant and chronic ventilator-dependent respiratory failure was transferred to our intensive care unit from an outside hospital for encephalopathy and acute kidney injury (presenting creatinine 3.3 mg/dL). Upon arrival, her vital signs were blood pressures (BP) 96/57 mmHg, heart rate (HR) 60–63 bpm, respiratory rate 16 breaths per minute, temperature 33.4°C and SpO₂ 98% on continuous positive airway pressure with 28% FiO₂. Her physical examination was notable for being arousable only to painful

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stimuli, coarse breath sounds and diffuse bilateral edema in her upper and lower extremities. Her urine sediment showed many white blood cells, renal tubular epithelial cells, rare monomorphic red blood cells and no casts. She was treated empirically for sepsis with antimicrobials and intravenous (IV) albumin and underwent encephalopathy work-up, which was unremarkable. She had mild hyponatremia and other electrolyte abnormalities (Table 1).

The etiology of her kidney failure was unclear, and a kidney biopsy was not performed due to clinical instability. CRRT via a temporary catheter was initiated on hospital day 3 for volume overload in the setting of anuric kidney failure (creatinine 3.6 mg/dL) and hemodynamic instability. After a 15–30 minute normal saline prime, an NxStage (NxStage Medical, Lawrence, MA) machine with a gamma-sterilized polyethersulfone membrane (PUREMA[®], 3 M, Charlotte, NC) was used. At CRRT start, her BP was 147/66 mmHg and HR 65 bpm. However, within 5 minutes of CRRT initiation, her BP fell to 70/30 mmHg. At the time of the hypotensive event, the

blood flow and ultrafiltration rates were 200 and 10 mL/h, respectively. Blood flow was stopped, supportive measures including supplemental oxygen, IV fluid, and norepinephrine infusion were administered. Her BP improved and CRRT was restarted. However, she developed recurrent hypotension within 5 minutes and eventual loss of pulse. CRRT was stopped, blood returned, and patient resuscitated with chest compressions, IV fluid, two doses of IV epinephrine and norepinephrine infusion.

Twenty-four hours later, she was treated with HD using a Fresenius 2008T machine (Fresenius Medical Care, Waltham, MA) and an EXELTRA[®] (Baxter Healthcare Corporation, Deerfield, IL) dialyzer, a high-flux, single-use, gamma radiation sterilized dialyzer composed of cellulose triacetate. Prior to treatment, the dialyzer was flushed with 2 liters of normal saline, and the patient was medicated with methylprednisolone sodium succinate, diphenhydramine, and famotidine. She again developed vasopressor-requiring hypotension within 5 minutes of treatment start, and HD was terminated, but blood was not returned. The next day, she was treated with HD using an NxStage machine with a Streamline Express[®] (B. Braun Medical, Inc., Bethlehem, PA) dialyzer, a gamma radiation sterilized polyethersulfone membrane with preattached blood tubing set. She tolerated this session without complication. All treatments were heparin-free; she was not receiving an angiotensin converting enzyme inhibitor (ACEI); and she had no evidence of allergy to latex or antiseptic at other times during the hospitalization.

Table 1 Relevant laboratory values

	Admission	Preinitial CRRT event	Postinitial CRRT event
Serum electrolyte and complete blood count			
White blood cell count (n/L)	4.8	10.4	6.2
Hemoglobin (g/dL)	7.3	7.6	8
Platelets (n/L)	213	172	173
Sodium (mEq/L)	130	131	133
Potassium (mEq/L)	5.1	4.6	4.6
Bicarbonate (mEq/L)	36	35	32
Creatinine (mg/dL)	3.2	3.6	3.6
INR	1.1	—	—
Hypersensitivity markers			
C3 (mg/dL)	—	—	87
C4 (mg/dL)	—	—	19.7
Eosinophil absolute count (μL)	0.1	0.1	0.0
Lactate, arterial (mmol/L)	0.6	5.7	—
Total IgE (kU/L)	—	—	<2.00
Ethylene oxide IgE (kU/L) ^a	—	—	<0.35*

Abbreviation: IgE, immunoglobulin E.

^aDrawn 20 days after the initial CRRT treatment.

DISCUSSION

This patient had severe hypotensive episodes during dialysis most consistent with dialysis-associated hypersensitivity reactions. While she was critically ill prior to dialysis treatment, she acutely worsened within minutes of dialysis initiation and improved when blood circulation through the machine was halted. The immediate improvement of her BP following treatment cessation makes sepsis or other acute illnesses unlikely. She received no medications likely to be implicated in the reactions. The dialysate used for the CRRT treatment was from premixed manufacturer-made bags (NxStage Dialysate Sack (SAK) with concentrate), and the use of dialysate from the same lot was uneventful in other patients. No other patients treated at the same time and with the same water source experienced reactions, and there were no known issues with the local water system. Clinical suspicion for dialysis-associated allergic reactions led the

nephrology team to select different machines and dialyzers for future dialysis treatments to prevent reexposure to the yet unidentified allergen.

Dialysis-associated allergic reactions are classified as Type A or Type B reactions.^{2,3} Type A reactions typically occur within 5–20 minutes of dialysis initiation whereas Type B reactions are usually delayed and occur later in the session. Type A reactions are IgE-mediated (i.e. anaphylactic), attributed to preformed antibodies against an allergen. In these reactions, IgE activates effector cells (e.g. mast cells and basophils), causing the release of preformed mediators (e.g. histamine), arachidonic acid metabolites (e.g. leukotriene, prostaglandin), and cytokines, which can lead to symptoms of pruritus, urticaria, bronchospasm and/or anaphylactic shock.⁴ Type B reactions are non-IgE-mediated (i.e. anaphylactoid), triggered by either direct triggers or complement activation and usually produce less intense and self-limited symptoms such as back and/or chest pain. As symptoms from Type A and B reactions can overlap as well as mimic other illnesses, additional laboratory investigation is needed to confirm diagnosis and identify the offending allergen.

Multiple precipitants must be considered when evaluating potential dialyzer reactions—the dialyzer membrane, sterilizing agent, disinfectant, antiseptics, medications, and all aspects of the dialysis circuit that interface with blood.^{5,6} Some important allergens associated with dialyzer reactions include latex, ethylene oxide (EtO), heparin, iron, angiotensin-converting enzyme (ACE) inhibitors, and polyacrylonitrile membrane (PAN AN69®). In prior eras, hypersensitivity reactions to cellulose membranes were common, but the incidence of these reactions has declined with the advent of synthetic membranes.⁷ However, hypersensitivity reactions to synthetic membranes may be on the rise^{4,6,8} and thrombocytopenic reactions to dialyzers sterilized by electron-beam have been reported.⁹ Hypersensitivity markers of interest include eosinophil absolute count and percentage, tryptase, total immunoglobulin E (IgE), C3 and C4, though timing and duration of elevation of such markers vary.^{10,11} Elevated total serum IgE levels during dialyzer reactions are well reported and allergen-specific IgE presence can help confirm the precipitating agent.^{4,5} For example, EtO IgE has been documented in cases of anaphylactic reactions to the sterilizing agent, EtO.^{5,12} EtO, a potent alkylating agent used in gas sterilization of dialysis membranes, can cause Type A anaphylactic dialyzer reactions and has been widely documented as one of the most common precipitating allergens.^{13,14}

We believe our patient experienced Type A hypersensitivity reactions during CRRT and HD, both using

Table 2 Dialyzer, tubing, and bloodline ancillary component properties

Dialyzer	Reaction in case	Modality	Manufacturer	Membrane type	Membrane sterilization	Tubing manufacturer	Tubing sterilization	Bloodline ancillaries	Bloodline ancillaries ^a sterilization
PUREMA H®	Yes (x2)	CRRT	3M	Polyethersulfone	Gamma radiation	Fresenius medical care	Gamma radiation	—	—
EXELTRA®	Yes	HD	Baxter healthcare	Cellulose triacetate	Gamma radiation	Fresenius medical care	Ethylene oxide	Fresenius medical care	Ethylene oxide
Streamline®	No	HD	NxStage/Fresenius medical care	Polyethersulfone	Gamma radiation	NxStage/fresenius medical care	Gamma radiation	—	—
Optiflux®	Not used	HD	Fresenius medical care	Polysulfone	Electron beam	Fresenius medical care	Ethylene oxide	Fresenius medical care	Ethylene oxide
F180NR®									

Abbreviations: CRRT, continuous renal replacement therapy; HD, hemodialysis.

^aTransducer protector from CombiSet® true flow bloodlines.

dialyzers that were gamma radiation sterilized (Table 2). The event timing and severity support this diagnosis, but serum hypersensitivity markers were inconclusive (Table 1). The first dialyzer was a polyethersulfone membrane with gamma-sterilized tubing, and the second dialyzer was a cellulose triacetate membrane. Postevent investigation revealed that the tubing (Combiset® True Flow Bloodlines tubing, Fresenius Medical Care, Waltham, MA) and at least one of its ancillary components (the transducer protector) used in the latter instance was sterilized with EtO. Serum EtO IgE was drawn 20 days after the initial reaction and was negative. False-negative results for allergen-specific IgE have been reported up to 3.5 weeks after exposure.¹⁵

We initially thought the reaction might be related to the NxStage machine. There are reports of hypotension from unclear causes on NxStage machines on the U.S. Food and Drug Administration's (FDA) Manufacturer and User Facility Device Experience (MAUDE) website (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/TextSearch.cfm>, Figure 1). However, the event recurred on a Fresenius Medical Care-manufactured machine, rendering a machine-triggered reaction less likely. We can only hypothesize as to the cause of her reaction; possibilities include exposure to EtO or another antigen within the system or a reaction to the membrane itself. The patient eventually tolerated a different polyethersulfone membrane with pre-

A. MAUDE - Manufacturer and User Facility Device Experience

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Product Problem

Product Class

Event Type Manufacturer

Model Number Report Number

Brand Name Product Code

Date Report Received by FDA (mm/dd/yyyy) to

[Go to Simple Search](#) Records per Report Page [Clear Form](#)

B. 1 to 10 of 10 Results for NxStage and hypotension 2018

results per page

New Search Export To Excel Help		
Manufacturer	Brand Name	Date Received
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	11/29/2018
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	11/29/2018
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	11/02/2018
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	10/26/2018
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	08/31/2018
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	08/31/2018
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	05/31/2018
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	05/18/2018
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	03/28/2018
NXSTAGE MEDICAL, INC.	NXSTAGE SYSTEM ONE	03/15/2018

Figure 1 FDA manufacturer and user facility device experience (MAUDE) system. Panel A displays the advanced search interface from the FDA MAUDE website (<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Search.cfm>). Panel B displays results (N = 10) from a query of “NxStage and hypotension” in calendar year 2018 performed on August 27, 2019. Abbreviation: FDA, food and drug administration. [Color figure can be viewed at wileyonlinelibrary.com]

attached gamma-sterilized blood tubing set, further pointing to the tubing or its ancillary components as the allergen source.

CONCLUSIONS

Dialysis-associated reactions are rare but potentially life-threatening complications of dialysis. This report underscores the importance of rapid recognition, treatment, and investigation of dialyzer reactions. In this case, the patient's blood was returned during her initial reaction, potentially contributing to its severity. In cases of suspected dialyzer reactions, it is imperative that dialysis be stopped immediately and blood not returned. The case also highlights the importance of investigating all components of the RRT set-up, including the tubing and its ancillary components, when a dialysis-associated reaction is suspected. While none of the dialyzers was EtO sterilized, the tubing and some of its ancillary components were sterilized with EtO. In all suspected reactions, the machine tubing, needle and dialyzer should be saved, machine number, and dialyzer lot number recorded, and, in some cases, dialysate fluid cultured for bacterial contamination. Serum hypersensitivity markers should be drawn to confirm the allergic nature of the reaction. The event should be clinically and administratively documented to facilitate monitoring for clusters of similar events; root cause analysis undertaken; and the biomedical team should inspect the machine. If a dialyzer reaction is strongly suspected, testing for specific antibodies is important for allergen identification. In the meantime, a different dialysis method or membrane should be used for subsequent treatments. In some cases, event documentation in the FDA MAUDE system may be appropriate to facilitate recognition of potential manufacturing issues that would likely go unnoticed at single centers.

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